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Investigating the most appropriate dose and effectiveness of thiotepa in combination with ifosphamide, etoposide and rituximab in patients with lymphoma arising in the brain or spinal cord

Submission date 03/12/2014	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 03/12/2014	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 15/02/2023	**Condition category** Cancer	[_] Individual participant data

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-chemotherapy-and-biological-therapy-for-lymphoma-of-the-brain-or-spinal-cord-tier

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2014-000227-24

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
17668

Study information

Scientific Title
A study of thiotepa, ifosphamide, etoposide and rituximab for the treatment of relapsed or refractory primary central nervous system lymphoma

Acronym
TIER

Study objectives
The phase I dose finding component is a 3+3 cohort design which will recruit up to 18 patients in order to find the MTD of thiotepa in combination with ifosphamide, etoposide and rituximab (TIER). All patients recruited into phase I at the MTD will also contribute towards phase II. The phase II study is based on an A'Hern’s design to assess the activity of thiotepa in combination with ifosphamide, etoposide and rituximab (TIER). 28 patients will be recruited in total in phase II (including some patients from phase I).

Ethics approval required
Old ethics approval format

Ethics approval(s)
14/LO/1568; First MREC approval date

Study design
Non-randomised, interventional

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Primary central nervous system lymphoma

Interventions
Etoposide, 250mg/m2 day 2 of 21 day cycle; Ifosphamide, 2g/m2/day days 2-4 for each 21 day cycle.; Rituximab, 375mg/m2/day days 1-2 for each 21 day cycle; Thiotepa, Chemotherapy (doses 20mg/m2 - 50mg/m2)

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
1. Etoposide 2. Ifosphamide 3. Rituximab 4. Thiotepa

Primary outcome measure
MTD of thiotepa in combination with ifosphamide, etoposide and rituximab (TIER)
Timepoint(s): End of 2 cycles of treatment

Secondary outcome measures
1. 2 year event free survival (EFS); Timepoint(s): 2 years after trial treatment
2. 2 year overall survival (OS); Timepoint(s): 2 years after trial treatment
3. 2 year progression free survival (PFS); Timepoint(s): 2 years after trial treatment
4. CR rate after 2 cycles of TIER; Timepoint(s): End of 2 cycles of treatment
5. Overall response rate (Complete Response (CR) + Complete Response: unconfirmed (CRu) + Partial Res; Timepoint(s): end of 2 cycles of treatment
6. Proportion of patients proceeding to high-dose therapy and autologous stem cell transplant (HDT-AS; Timepoint(s): Following trial treatment
7. Rate of successful stem cell harvest; Timepoint(s): After completing trial treatment
8. Toxicity of TIER using the National Cancer Institute Common Terminology Criteria for Adverse Event; Timepoint(s): All cycles of trial treatment

Overall study start date
12/12/2014

Completion date
31/10/2021

Eligibility

Key inclusion criteria
1 Age ≥ 16 years of age
2. Histologically confirmed* CD20+ Diffuse Large B Cell Lymphoma (DLBCL) confined to the central nervous system
3. Relapsed or refractory primary central nervous system lymphoma (PCNSL) according to the following definition :
3.1. One or two prior chemotherapy regimen(s), of which at least one regimen contained highdose

methotrexate at a dose of >1g/m2.
3.2. Minimum of one cycle containing highdose methotrexate
4. ECOG performance status 0,1 or 2 (or 3 if attributed to lymphoma)
5. Adequate organ function:
5.1. Bone marrow: platelets >80 x109/L, neutrophils >1 x109/L, haemoglobin >80 g/L
5.2. Hepatic: bilirubin <1.5 x upper limit of normal (ULN) (unless isolated unconjugated hyperbilirubinaemia attributable to Gilbert's syndrome)
5.3. Renal: eGFR ≥40ml/min (Cockcroft-Gault)
5.4. Cardiorespiratory (as judged by the Local Investigator): clinically relevant cardiac or pulmonary function tests must be performed if there is a previous history of significant cardiac or pulmonary impairment
6. Able to comply with the scanning requirements of the study
7. Valid Informed consent

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 40; UK Sample Size: 40

Total final enrolment
36

Key exclusion criteria
1. Systemic involvement with lymphoma
2. Active infection requiring intravenous antimicrobials
3. Chemotherapy for lymphoma within 4 weeks registration
4. Wholebrain radiotherapy within 6 months of registration
5. Relapse within 1 year of a Thiotepabased autologous stem cell transplant
6. Prior therapy with the RIE (Rituximab – ifosphamide and etoposide) regimen
7. Evidence of HIV or Hepatitis C infection
8. Hepatitis B infection*
9. Serum albumin <25g/l
10. Pregnant and lactating patients (patients of childbearing potential must have a negative pregnancy test prior to study entry)
11. Competent pPatients and competent patients with partners of childbearing potential not willing to use effective contraception during and for 12 months after therapy

Date of first enrolment
12/12/2014

Date of final enrolment
30/04/2019

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Cancer Research UK Clinical Trials Unit
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Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
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United Kingdom
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Study participating centre
Aberdeen Royal Infirmary
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AB25 2ZN

Study participating centre
Beatson West of Scotland Cancer Centre
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United Kingdom
G12 0YN

Study participating centre

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London
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SE5 9RS

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St James University Hospital
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LS9 7TF

Study participating centre
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L9 7AL

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The Christie
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M20 4BX

Study participating centre
Freeman Hospital
Newcastle
United Kingdom
NE7 7DN

Study participating centre
Nottingham City Hospital
Nottingham
United Kingdom
NG5 1PB

Study participating centre

Churchill Hospital
Oxford
United Kingdom
OX3 7LE

Study participating centre
Derriford Hospital
Plymouth
United Kingdom
PL6 8DH

Study participating centre
University College Hospital
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NW1 2BU

Study participating centre
The Royal Marsden Hospital
Sutton
United Kingdom
SM2 5PT

Study participating centre
Royal Hallamshire Hospital
Sheffield
United Kingdom
S10 2JF

Study participating centre
Southampton General Hospital
Southampton
United Kingdom
SO16 6YD

Study participating centre

New Cross Hospital
Wolverhampton
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WV10 0QP

Sponsor information

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University of Birmingham

Sponsor details
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Sponsor type
University/education

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
Leukaemia and Lymphoma Research

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date
31/10/2022

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Plain English results			25/10/2022	No	Yes
Basic results		15/02/2023	15/02/2023	No	No
Results article		26/10/2021	15/02/2023	Yes	No
HRA research summary			28/06/2023	No	No